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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,544	04/27/2001	Defu Zeng	STAN 190	3043

24353 7590 05/09/2005

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ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

MAILED

MAY 0 9 2005

GROUP 1600

Application Number: 09/844,544

Filing Date: April 27, 2001

Appellant(s): Zeng et al

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For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 31, 2005 appealing from the Office action mailed October 21, 2003.

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This is in response to the brief on appeal filed January 31, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is substantially correct, with the exception of the mailing date of the Restriction Requirement which is October 25, 2002 rather than October 2, 2002.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of invention contained in the brief is substantially correct; however, while the text of the first paragraph of summary of invention contained in the brief, exclusive of the last sentence of said paragraph, is correctly referenced to page 1 of the specification at lines 1-11, the reference for the last sentence of said first paragraph of summary of invention contained in the brief should be to page 7 of the specification at [0026].

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Amano et al. J. Immunol. 1998, 161: 1710-1717, IDS reference

Kotzin et al. Cell. 1996, 85 : 303-306, IDS reference

Zeng et al. J. Exp. Med. 1998, 187: 525-536

Blumberg et al. Immunol. Rev. 1995, 147: 5-29

Hughes, D. Drug Disc. Today. 1998, 3(10): 439-442

The Merck Manual of Diagnosis and Therapy. 16th Edition. Berkow, R. et al, Editors. 1992 : 1316-1321

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claims 1, 2, 6, 7, 8, 10 and 12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amano et al (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng et al (J. Exp. Med. 1998, 187: 525-536), Blumberg et al (Immunol. Rev. 1995, 147: 5-29) and Hughes (Drug Disc. Today 3(10): 439-442, 1998).

Amano et al teach that the interaction between anti-CD1 T cells and B cells expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG. Amano et al further teach that transgenic T cells specific for CD1 (Vβ9/Vα4.4 T cell clone) induce lupus (SLE, an autoimmune disease) when transferred into nude host mice that do not spontaneously develop lupus, that these nude mice develop anti-ds DNA antibodies, proteinuria and ascites, and additionally, that the transgenic T cells could activate wild-type BALB/c B cells via the cross-linking of cell surface CD1 to secrete both IgM and IgG *in vitro*. Amano et al teach that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11. Amano et al teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (i.e., mice that spontaneously develop disease) is mediated by the $CD1^{hi}$ subset of B cells, "More recent studies have shown that the spontaneous secretion *in vitro* of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White [i.e., NZB/NZW] mice is mediated by the CD1 high subset of B cells" (i.e., that spontaneous antibody secretion in the same disease model used by Applicant is mediated by CD1 positive B cells) (especially second to last paragraph of article). Amano et al teach that CD1 by itself or in combination with endogenous antigens appears to be recognized by an autoreactive subset of T cells expresing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the vα14Jα281 associated with Vβ2,

Vβ7 or Vβ8 receptors, but that Tcells that express neither the NK1.1 marker nor the Vα14 TCR are able to recognize CD1 on syngeneic antigen presenting cells (especially column 2 on page 1710 at the first paragraph).

Amano et al do not teach the claimed method of treating pathogenic polyclonal B cell activation or class switching, including that resulting in lupus (SLE), in a patient, comprising administering a CD1 blocking agent that is an antibody, including a monoclonal antibody.

Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing B cells (i.e., pathogenic polyclonal B cell activation), a process that mimics a normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG class switching (especially first paragraph on page 304). Kotzin teaches that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE (especially last paragraph on page 303). Kotzin et al further teach that T cells are clearly involved in the development of autoantibody production in SLE (especially column 1 on page 303 at the 2nd to the last sentence in column 1).

Zeng et al teach T cells with transgenic TCR that recognized CD1 of syngeneic B cells induced lupus with resulting anti-ds DNA autoantibodies, proteinuria and immune complex glomerulonephritis in nude mice that don't spontaneously develop lupus (especially abstract). Zeng et al teach anti-CD1 mAbs, including 3C11 (anti-CD1d) (especially materials and methods).

Zeng et al teach that severity of disease is associated with the development of the anti-ds DNA autoantibodies and with elevated serum IgG2a as has been observed with hereditary lupus (especially page 534 at the second full paragraph in column 1). Zheng et al teach that in hereditary murine lupus, administration of IL-10 worsens the disease and administration of anti-IL-10 antibodies ameliorates the disease likely through regulation of TNF-α secretion since endogenous TNF-α is increased in lupus after the injection of the anti-IL-10 antibodies. Zeng et al teach that in hereditary murine lupus, administration of IFN-γ worsens lupus, and the injection of anti-IFN-γ antibodies ameliorates the disease, and that IFN-γ and IL-10 on one hand, and TNF- α on the other, play opposing roles in regulating the disease (especially paragraph spanning columns 1 and 2 on page 534). Zeng et al teach that both $CD4^+$ and $CD4^- CD8^-$ T cells from the spleen of mice with hereditary lupus have been reported to augment the secretion of anti-ds DNA antibodies *in vitro* (especially the last sentence of the paragraph spanning columns 1 and 2 on page 533).

Zeng et al teach that SLE inducing cells, i.e., the single positive T cells, secreted large amounts of IFN-γ and little IL-4 (i.e., have a Th1 phenotype), and the SLE preventive cells, i.e., the double negative cells, secreted large amounts of IL-4 (i.e., have a Th2 phenotype) and little IFN- γ and little IL-10 (especially page 525 first column and abstract). Zeng et al further teach that introduction of an IL-4 transgene (encodes a Th2 cytokine) into NOD or NZW X C57BL/6 mice prevents SLE. Zeng et al teach "It is not surprising that T cells that secrete high levels of IFN- γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 $CD4^+$ cells may induce or worsen lupus after

activation of their CD1 receptors. One the other hand, the transgenic BM $CD4^-CD8^-$ T cells that secrete high levels of IL-4 and low levels of IFN-γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern" (especially paragraph spanning columns 1 and 2 on page 534). Zeng et al also teach "The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical". "...NZB/NZW F1 mice [the same model of spontaneous lupus disclosed by Appellants in the instant specification] lose a subset of T cells..that recognizes CD1 and secretes high levels of IL-4 just before lupus develops. Anti-Vα14 monoclonal antibodies injected into MRL/lpr mice exacerbates the development of lupus, and depletes this T cell subset...The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the CD4-CD8- T cell subset in the marrow that prevented lupus in this study (especially paragraph spanning columns 1 and 2 on page 534). Zeng et al teach that "the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to the activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo." Zeng et al teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, i.e., the anti-ds-DNA antibodies for example, in lupus is via T cell recognition of the CD1 molecule (especially page 532 at the first paragraph of the second column).

Blumberg et al teach that CD1c is expressed on human B cells in peripheral blood, spleen and tonsil, that CD1a, b and c are expressed on activated monocytes (GM-CSF+/- IL-4), CD1a is expressed on Langerhans cells, CD1a, b and c are expressed on dendritic cells in the dermis and CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels (especially pages 14 and 15). Blumberg et al teach antibodies to the CD1 molecules, including 3C11 (anti-CD1d) and antibodies to CD1a, b and c. Blumberg et al further teach that 3C11 blocks the interaction of T cells with CD1d (especially second paragraph on page 23). Blumberg et al teach that 3C11 cross-reacts with human CD1d (specially page 14 at the last paragraph).

Hughes teaches administration of monoclonal blocking antibodies (such as anti-TNFα), including humanized or human antibodies, to patients for a variety of conditions including autoimmune disease. Hughes teaches that the conventional route to derive monoclonal antibodies has been to immunize mice, that these antibodies have widespread applications in research but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Hughes et al teach that use of humanized or human antibodies avoids such undesirable immune responses (especially page 439).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng et al or Amano et al or the anti-CD1a, b, c and d antibodies taught by Blumberg et al to block CD1 recognition by T cells as taught by Amano et al by administration of antibodies to subjects with SLE, and hence to treat pathogenic polyclonal B cell activation or class switching taught by Kotzin, including with humanized versions of the said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (iv) route of administraton as taught for administration of T cells by Zeng et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation or class switching in a patient with SLE with a reasonable certainty of success because:

(1) Amano et al teach that interaction between anti-CD1 T cells and B cells that express cell surface CD1 leads to mutual activation of both cell types that results in systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG and that T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11, that transgenic anti-CD1 T cells can induce SLE with resulting anti-ds DNA antibodies, proteinuria and ascites when transferred into nude host mice that do not spontaneously develop the disease, and that the transgenic T cells could activate wild-type BALB/c B cells via the mechanism of cross-linking cell surface CD1 to secrete both IgM and IgG *in vitro*, and Amano et al correlate these teachings with the teaching that spontaneous secretion of IgM and IgG

by splenic B cells from lupus-prone NZB/NZW mice (i.e., mice that spontaneously develop disease) is mediated by the $CD1^{hi}$ subset of B cells;

(2) Kotzin et al teach that pathogenic IgG autoantibody production in SLE occurs by clonal expansion of somatically mutated anti-DNA antibody-producing B cells, i.e., by pathogenic polyclonal B cell activation, said activation involving the mechanisms of affinity maturation and IgM to IgG class switching, that T cells are clearly involved in the development of autoantibody production in SLE, and that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis in SLE;

(3) Zeng et al teach that T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice, said mice developing anti-ds-DNA autoantibodies, proteinuria and immune complex glomerluonephritis, that the severity of disease in this experimental system is associated with the anti-ds DNA autoantibodies and with elevated serum IgG2a as it is in mice with hereditary lupus, that T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce disease or protect from disease depending upon their cytokine profile, i.e., disease inducing cells secreted large amounts of IFN-γ and little IL-4 whereas disease protective cells secreted large amounts of IL-4 and little IFN-γ or IL-10, that the cytokine secretion patterns of T cells plays a critical role in regulating B cell activation, that these teachings correlate with hereditary murine lupus in that administration of IL-10 or IFN-γ worsens the disease, whereas administration of anti-IFN-γ or anti-IL-10 antibodies ameliorates the disease, that both single positive and double negative T cells from these mice have been reported to

augment the secretion of anti-ds DNA autoantibodies *in vitro*, that introduction of IL-4 transgene into NOD or NZW X C57BL/6 mice prevents SLE, that administration of antiVα14 (i.e., anti-TCR) mAbs to MRL/lpr mice exacerbates the development of lupus because it depletes a subset of T cells that recognize CD1 and secrete a high level of IL-4, that in NZB/NZW mice (i.e., in the same model of spontaneous lupus disclosed by Appellants) said mice lose a subset of T cells with the same characteristics of recognizing CD1 and secreting high levels of IL-4 just before disease develops;

(4) Zeng et al, Amano et al and Blumberg et al teach anti-CD1 mAbs, Blumberg et al further teach CD1 expression on various tissues and cells in the body including B cells and antibodies to CD1, including rat anti-mouse CD1d mAb 3C11 that cross-reacts with human CD1d;

(5) Hughes teaches the administration of monoclonal blocking antibodies such as anti-TNFα to patients to treat a variety of conditions including autoimmune diseases and that it is advantageous when treating human patients to use humanized rodent antibodies to avoid undesirable immune reactions to the foreign nature of the rodent antibodies.

Claim 12 is included in this rejection because the intravenous (iv) route of administration was well known in the art at the time the invention was made and Zeng et al teach intravenous administration of T cells, so it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have injected the antibody/ies via the iv route of administration. Claim 8 is included in the instant rejection because the CD1d antibodies taught by Zeng et al or Amano et al would be expected to bind to human CD1d since CD1d of mice or rat would be expected to cross-

react with human CD1d due to the high degree of homology between mouse, rat and human CD1d and as taught by Blumberg et al for the rat anti-mouse 3C11 antibody that cross-reacts with human CD1d. Alternately, the value of monoclonal antibodies to proteins was well known in the art at the time the invention was made, in terms of specificity, purity and yield, and Blumberg et al teach the human CD1d protein. A routineer would have used the same basic technique for producing monoclonal antagonist antibodies against human CD1d protein by using an appropriate *in vitro* assay where antagonistic antibodies could be detected.

II. Claim 13 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Amano et al (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng et al (J. Exp. Med. 1998, 187: 525-536), Blumberg et al (Immunol. Rev. 1995, 147: 5-29) and Hughes (Drug Disc. Today 3(10): 439-442, 1998) as applied to claims 1, 2, 6, 7, 8, 10 and 12 above, and further in view of the Merck Manual (pages 1317-1321, 16th Edition, 1992).

The combination of Amano et al, Kotzin, Zeng et al, Blumberg et al and Hughes has been discussed supra, “the combined references”.

The “combined references” not teach the claimed method of treatment of activation/class switching that results in SLE recited in instant claim 13 that further comprises administration of a second therapeutic agent for the treatment of SLE, including wherein the second therapeutic agent is an anti-inflammatory agent.

The Merck Manual teaches treatment of SLE with corticosteroid treatment (a class of anti-inflammatory agents), such as with prednisone, in combination with immunosuppressive agents. The Merck Manual teaches that severe disease with renal damage requires immediate corticosteroid therapy in combination with immunosuppressives, and that in both mild and severe disease, after the inflammatory response is controlled, the minimal dose of corticosteroids and other agents necessary to suppress tissue inflammation must be determined and administered, and that anticoagulant therapy is vital in patients with antiphospholipid antibodies and recurrent thrombosis (especially first three full paragraphs on page 1320, last said full paragraph continuing on to page 1321).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered along with the immunosuppressive agent that is the antibody to CD1 that blocks binding of the TCR to CD1 taught by the "combined references" an anti-inflammatory corticosteroid such as prednisone and/or the anti-coagulant taught by the Merck Manual for treatment of SLE.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively treat SLE by suppressing the immune system by blocking CD1-mediated pathogenic polyclonal B cell activation or class switching as taught by the "combined references" and to control the inflammatory response using corticosteroid(s) in combination with immunosuppressive agents as taught by the Merck Manual, and to treat with anti-coagulant agents in patients with antiphospholipid antibodies and recurrent thrombosis as is taught by the Merck Manual

as being vital for those patients. In addition, motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their <u>common known purpose</u>. Section MPEP 2144.07.

(10) Response to Argument

I. Appellant's arguments have been fully considered, but are not persuasive.

Appellant's arguments are of record, namely: (1) that Appellants have demonstrated *in vivo* blocking of CD1 by administration of antibodies significantly reduced the peak levels of serum IgG and IgG anti-ds autoantibodies and delayed disease progression in a spontaneous disease model representative of clinical disease [i.e., in NZB/NZW mice]; (2) that the teachings of the primary reference Amano et al as well as that of Zeng et al relate to work in animals that were made to be transgenic for a TCR that recognizes CD1, and these animals do not develop spontaneous disease [i.e., SLE], and that specific subpopulations of transgenic T cells from said animals can be transferred to cause disease, but that others that are more representative of native populations suppress disease; (3) that although the art suggested a possible connection between CD1 and SLE, there was substantial uncertainty that CD1 had a positive role, and without the findings in the instant application, one of skill in the art could not have had a reasonable certainty of success in practicing the claimed methods; (4) that some instances of prior art teaches away from the present invention with regard to the belief that NKT cells were protective for lupus, not causative, and Appellants cite Takeda et al, 1993, J. Exp. Med. 177: 155; (5) that because Amano et al Zheng et al use a

transgenic animal model that possess artificial features, one could not draw any conclusions with reasonable certainty about the role of CD1 in lupus, i.e., that the subset of cells that express the transgene are an important point, those said subsets not being restricted to NK T cells but also including conventional T cells, and the cells could be double negative in one mouse or single positive in another mouse; (6) that different T cell populations expressing the same TCR when expressed as a transgene could be either protective of disease or disease causing when transferred to a secondary animal host, while the transgenic mice did not develop disease; (7) that the secondary references Blumberg, Kotzin and Hughes fails to demonstrate the effectiveness of blocking CD1 to treat lupus-like disease.

It is the Examiner's position that: (1) Amano et al as well as Zeng et al correlate their teachings using experimental models different from Applicant's with teachings that do use the same experimental model as Applicant's as well as with teachings relating to hereditary murine SLE and to other models of hereditary murine SLE, for example the MLR/lpr mouse model; (2) Zeng et al recognize that their transgenic mice (or euthymic hosts) developed symptoms of SLE but they did not develop overt SLE due to the contribution of endogenous non-transgenic T cells that effectively competed with the transgenic T cells, i.e., that the antigen-induced expression of transgenic cells is markedly inhibited by the presence of the thymus in the adoptive hosts, thus necessitating transfer of the transgenic T cells into nude mice (especially page 533 at the first full paragraph at column 2); (3) One of ordinary skill in the art at the time the

invention was made would have had a reasonable expectation of success in practicing the claimed invention for the reasons of record and that Amano et al and Zeng et al teach that the interaction between anti-CD1 positive T cells and B cells expressing cell surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulineamia and systemic autoimmunity *in vivo* via cross-linking of CD1 on B cells to secrete IgM and IgG, and Amano et al teach that this proliferation could be inhibited with use of anti-CD1 monoclonal antibody *in vitro*; (4) the Takeda et al reference is not of record, has not been provided by Appellants and accordingly has not been considered by the Examiner. In addition, Takeda et al 1993 publication date is significantly prior to that of the cited art references, and that the cited art references teach that the cytokine profile of the responding T cell is the important factor over phenotype of the cell. In addition, the instant claims do not recite NK Tcells; (5) Amano et al teach that other T cells besides NK T cells with the restricted $V\alpha14$ $J\alpha281/V\beta7$ or $V\beta8$ T cell receptor recognize CD1 on syngeneic antigen presenting cells; (6) Zeng et al teach that the CD4/CD8 phenotype of the T cell is not the important consideration, but is rather the cytokine profile of the T cell that bears the TCR specific for CD1, and that the issue of protection vs induction of SLE hinges on the cytokine profile of the T cell; and (7) Appellants are arguing these references separately.

II. Appellant's arguments have been fully considered, but are not persuasive, i.e., that the invention of claim 13 is not made obvious by the cited combination of references because the prior art does not provide a reasonable expectation that administration of [anti-] CD1 would be effective in treating lupus-like disease, and that the inclusion of a second therapeutic regimen is not relied upon for patentability, but is merely put forth as a variation on Appellants methods.

It is the Examiner's position that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for the reasons of record in the rejection over Amano et al, Kotzin, Zeng et al, Blumberg et al and Hughes enunciated supra, and the Examiner's arguments thereto apply herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Marianne DiBrino

Marianne DiBrino, Ph.D.

April 29, 2005

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